November 27, 2002

Dr. Anne P. LeHuray
Technical Contact
The American Chemistry Council
Rubber and Plastic Additives Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. LeHuray:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Substituted Diphenylamines Category posted on the ChemRTK HPV Challenge Program Web site on January 15, 2002. I commend the Rubber and Plastic Additives Panel for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Substituted Diphenylamines Category

SUMMARY OF EPA COMMENTS

The sponsor, the Rubber and Plastic Additives (RAPA) Panel of the American Chemistry Council (ACC), submitted a test plan and robust summaries to EPA for the substituted diphenylamines category dated December 20, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 15, 2002. The category consists of eight sponsored substances and one supporting chemical.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals under this category may not be adequate for physicochemical properties and most of the health effect endpoints.

2. Physicochemical Properties and Environmental Fate. Adequate data are available for all SIDS-level endpoints except melting point and boiling point. The submitter needs to provide melting point and boiling point values for some members of the category.

3. Health Effects. The available data are adequate for the acute toxicity endpoint for the purposes of the HPV Challenge Program. EPA questions the category for the other SIDS-level health effect endpoints because the justification does not adequately account for existing toxicity data. In terms of the data provided for diphenylamine (from which most of the extrapolation is proposed to occur): (a) adequate data were submitted for acute, repeated-dose, genetic (mutation) and developmental toxicity for the purposes of the HPV Challenge Program. However, some of the robust summaries lack important information. (b) Although the submitted robust summaries for reproductive toxicity and genetic (chromosomal effects) are inadequate, diphenylamine is a registered pesticide and adequate robust summaries for these endpoints exist in the EPA Reregistration Eligibility Document (RED). (c) The RED may be consulted in this case as a reasonable summary of all SIDS-level health effect endpoints.

4. Ecological Effects. EPA agrees that no further testing is needed for the purposes of the HPV Challenge program. As the eight sponsored substances have high estimated log Kow values (>8), acute toxicity is not expected at or below their water solubility. Given that the proposed supporting substance diphenylamine has an estimated log Kow of <4 and is acutely toxic to aquatic organisms EPA did not consider it a useful part of the evaluation.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE SUBSTITUTED DIPHENYLAMINES CATEGORY CHALLENGE SUBMISSION

General

The submitter needs to provide the chemical composition (major components and their percentages) for those substances that are mixtures. The submitter also needs to indicate clearly that the alkyl substituents for CAS Nos. 101-67-7 and 36878-20-3 are branched as implied.

Category Definition

The submitter proposed a category covering nine N-phenylbenzenamines (diphenylamines), varying in the degree of alkyl and alkaryl substitution on the phenyl groups. The substances covered under the category are: N-phenylbenzenamine, reaction products with 2,4,4-trimethylpentene (CAS No. 68411-46-1); , styrenated N-phenylbenzenamine (CAS No. 68442-68-2); N-phenylbenzenamine, reaction products with 2,4,4-trimethylpentene and isobutylene (CAS No. 184378-08-3); 4-(1,1,3,3-tetramethylbutyl)-N-(4-(1,1,3,3-tetramethylbutyl)phenyl)benzenamine (CAS No. 15721-78-5); 4-octyl-N-(4-octylphenyl)-benzenamine (CAS No. 101-67-7); ar-nonyl-N-(nonylphenyl)benzenamine (CAS No. 36878-20-3); 2-ethyl-N-(2-ethylphenyl)benzenamine, (tripropenyl) derivatives (CAS No. 68608-77-5); and N-phenylbenzenamine, reaction products with styrene and 2,4,4-trimethylpentene (CAS No. 68921-45-9). The unsubstituted nonsponsored compound, N-phenylbenzenamine (diphenylamine, CAS No. 122-39-4), was included to provide data in support of the category. (NOTE: Diphenylamine is sponsored in the OECD SIDS program. However, the OECD data cannot be assumed to be adequate because data have not yet been reviewed at a SIDS Initial Assessment Meeting, or SIAM.)

Category Justification

The submitter states that the category is supported by the structural similarity between its members, which will result in similar physicochemical, environmental fate, and toxicological properties. Although the members of the category share a common N-phenylbenzenamine structure, they differ by the type and extent of substitution of the phenyl groups. The submitter needs to address this issue in the category justification. The test plan suggests that the common diphenylamine backbone is reason enough for the identified substances to constitute a category, and the test plan depends heavily on extrapolating available diphenylamine data to the eight sponsored substances. However, this requires a strong showing that significant substitution on the parent substance will not alter its toxicity. Some of the data suggest otherwise. For example, Table 2 suggests that some of the physicochemical properties (boiling point and partition coefficient) do not follow a pattern across the group of substances. Table 7 suggests that the repeated-dose data are reasonably similar for the three substances for which data are presented, but the robust summaries for diphenylamine and CAS No. 68921-45-9 show that different target organs are affected (primarily the kidney for diphenylamine and the liver for CAS No. 68921-45-9). There was no robust summary submitted for the data point indicated on the third chemical (styrenated N-phenyl-benzenamine).

Thus, EPA believes there is insufficient justification for considering the eight substances as a category for most of the health effect endpoints and for the use of supporting health effects data on diphenylamine.

For ecological effects, EPA finds a category approach plausible but the diphenylamine data not useful.

Test Plan

For some of the discussion below, EPA relies on the Office of Pesticide Programs EPA Reregistration Eligibility Document (RED) for diphenylamine - click on diphenylamine at the following URL: http://www.epa.gov/pesticides/reregistration/status.htm.

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

NOTE: Most of the category members are mixtures and estimating properties based on structure should be done for the expected range of structures in a mixture.

The submitted data for partition coefficient and water solubility are adequate for the purposes of the HPV Challenge Program.

Melting point. The submitter did not provide melting point data for CAS Nos. 68442-68-2, 68608-77-5, and 68921-45-9 and only provided an EPIWIN estimated value for CAS No. 15721-78-5. On page 2 of the test plan, the submitter indicates that all the chemicals in this category are "solids or viscous liquids", which suggests that their melting points may all be above 0 °C. OECD guidelines indicate that melting points need to be provided if they are greater than 0 °C. Furthermore, EPIWIN melting point estimations are in general not reliable. Therefore the submitter needs to provide measured data for these chemicals, unless it can show that their melting points are below 0 °C, in which case estimated data are acceptable. In the case of CAS No. 36878-20-3, the submitter indicates in Table 2 of the test plan that its melting point is less than 20 °C. However, in the robust summary the submitter did not provide a value. The submitter needs to provide a melting point for this chemical in robust summary format. Values from published literature sources are acceptable as long as the source is specified.

Boiling point. In Table 2 of the test plan the submitter indicates that the boiling points for CAS Nos. 68442-68-2 and 36878-20-3 are not known. According to OECD guidelines, if the boiling point is above 300 °C, then a specific value is not needed. If the submitter can't show that these substances boil at > 300°C, then the submitter needs to provide measured data.

Vapor Pressure. In Table 2 of the test plan the submitter indicates that the vapor pressure for CAS Nos. 68442-68-2 and 36878-20-3 are not known. According to OECD guidelines, if the vapor pressure is estimated to be less than 10^{-5} kPa at 25°C, then testing is not needed. If the submitter can't show this, then the submitter needs to provide measured data.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

The submitted information does not support extrapolation of the diphenylamine data to the eight sponsored substances, especially for the chromosomal effects, reproductive and developmental toxicity endpoints. Adequate data exist for acute toxicity (five of the nine substances) and no further testing is needed for this endpoint for the purposes of the HPV Challenge Program.

Repeated-Dose Toxicity. Submitted robust summaries on the repeated-dose toxicity of diphenylamine, the lowest molecular weight substance among the nine substances, indicate the kidney as a major target

organ. The RED provides extensive reviews on repeated-dose toxicity and identified the spleen as a major target organ for toxicity following exposure to diphenylamine. However, the single repeated-dose toxicity study of CAS No. 68921-45-9 only indicates adverse effects to the liver, and not the kidney or spleen. Table 7 shows a NOAEL from a 28-day oral repeated-dose toxicity study of CAS No. 68442-68-2. However, the submitted IUCLID data set does not include a summary for this study. Including this study in this submission would help to further characterize the repeated-dose toxicity for the proposed category approach. However, the available information suggests that diphenylamine behaves differently than at least one of the other substances and thus an extrapolation approach may not be appropriate for this endpoint.

Genetic Toxicity. There appear to be adequate available data to describe the potential for genetic mutations in bacteria (six of the nine substances tested). However, only three of the nine substances have been evaluated for the chromosomal endpoint (diphenylamine, CAS No. 101-67-7, and CAS No. 68442-68-2). Given the lack of justification for extrapolating diphenylamine data to the eight sponsored substances, the submitter needs to provide justification that existing data on two of the eight substances are sufficient to satisfy the data needs for the category for the purposes of the HPV Challenge Program.

Reproductive Toxicity. Reproductive toxicity data provided by the submitter for the supporting chemical diphenylamine were inadequate for the following reasons:

> (1) Four of the studies do not assess reproductive performance. These involved dosing one sex only and appeared to involve no mating (Wickramaratne 1987, referenced as numbers 22, 23, 24, and 82 in the IUCLID summary, and Korolev 1976), or the protocol was unclear about whether the hypothesis of the experiment was to evaluate reproductive performance at all (the Guinea pig study in Philbert, 1978).
>
> (2) The two other studies (De Eds, 1963 and the rat study in Philbert, 1978) could be supportive information, but neither one is sufficient to be a key study. Both involve unusual dosing and mating protocols that might not be appropriate.

In addition, the submitter did not report any NOAELs or LOAELs for reproductive toxicity in the test plan Matrix of Available and Adequate Data (Table 7). Thus, EPA believes the information presented for reproductive toxicity is not sufficient to address this endpoint.

However, a diphenylamine robust summary adequate for the purposes of the HPV Challenge Program (a 1993 two-generation study vs. the 1963 two-generation study identified above and in the submitted IUCLID data set for diphenylamine) has been developed in the EPA RED - click on diphenylamine at http://www.epa.gov/pesticides/reregistration/status.htm. Given this information, EPA believes that a new reproductive toxicity test is not necessary at this time.

Developmental Toxicity. Four of the six robust summaries submitted under the reproductive toxicity section for diphenylamine actually represent developmental toxicity data as exposures to the test substance occurred subsequent to mating (gestational exposures). These studies should be moved to the developmental toxicity section.

EPA believes that the test plan does not provide sufficient justification for extrapolating the diphenylamine results to all other category members because there are no supporting data available for other members.

Ecotoxicity (fish, invertebrates, and algae).

EPA believes that new aquatic toxicity data are not necessary at this time. The acute data submitted for some of the sponsored chemicals (CAS Nos. 68411-46-1, 68442-68-2, 101-67-7, and 36878-20-3) are

inadequate because substances were tested above their water solubility limits. However, all eight sponsored substances have calculated log Kow values (EPIWIN) above 8.0 and are expected to show no acute or chronic aquatic effects at or below their water solubility limits.

Thus, a category approach is reasonable (but not essential) for the eight sponsored chemicals. EPA did not consider the use of supporting data on diphenylamine (estimated log Kow <4) to be appropriate for these endpoints.

Specific Comments on the Robust Summaries

Physicochemical Properties

Vapor Pressure and Partition Coefficient. The submitter reports the same physicochemical data for two different substances, CAS Nos. 68411-46-1 and 184378-08-3. The remarks in the melting point section refer to butylated/octylated components which agrees only with the latter substance and the remarks in the vapor pressure section for 184378-08-3 state that "components for this chemical are the same as for CAS No. 68411-46-1". The submitter needs to clarify these discrepancies.

Environmental Fate

Biodegradation. In the IUCLID data set for CAS No. 68442-68-2, the submitter cited guideline "30 C" and indicates that the study type is anaerobic. OECD Guidelines 301 C and 302 C are for aerobic conditions. The submitter needs to state the complete guideline number and clarify these discrepancies.

Fugacity. In these calculations measured values for input parameters should be used when available.

Health Effects

NOTE: The following comments should be considered pending submitter's submission of an adequate justification for extrapolating diphenylamine health effects data to the other category members.

Overall, the robust summaries are adequate for acute, repeated- dose, genetic and developmental toxicity studies. However, the submitter needs to add missing study details to appropriate summaries as indicated below. Numbers of animals are missing from many summaries for all health effects endpoints. In addition, in many robust summaries, the reader is referred to sections 1.1-1.4 of the IUCLID data set for the identity of the test substance, which the submitter failed to include. It would be preferable for that information, with CAS registry numbers, to appear in the robust summary for each test.

Acute Toxicity. All of the summaries for diphenylamine and the oral toxicity study for CAS No. 68608-77-5 lack experimental details other than the species tested and the estimated lethal dose.

Repeated-Dose Toxicity. The summary of the 64-week study with CAS No. 68921-45-9 is missing the following information: severity and incidence of all effects noted.

Genetic Toxicity. Experimental details missing from some genetic toxicity study robust summaries include test concentrations (all the in vitro studies for diphenylamine), positive and negative controls (for most summaries), number of replicates, and statistical analyses. The summary for the rat dominant lethal assay with CAS No. 101-67-7 lacks the following information: doses and treatment regimen and the severity and incidence of effects observed (preferably compared to a positive control).

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

Editorial Comments

Figure 1 in the test plan is incorrect. It is given as R-Ph-N-R when it should be R-Ph-N-Ph-R' where R,R' = hydrogen, butyl derivatives, octyl derivatives, nonyl derivatives, or styrenyl, and R = R' = hydrogen is used as an analog.

Figure 2 in the test plan shows two of the structures twice.

The chemical name for CAS No. 184378-08-3 in Table 1 of the test plan is incorrect.